(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau





(43) International Publication Date 16 October 2003 (16.10.2003)

PCT

(10) International Publication Number WO 03/084543 A1

(51) International Patent Classification⁷: A61K 31/506, 31/445

(21) International Application Number: PCT/IB03/01418

(22) International Filing Date: 4 April 2003 (04.04.2003)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data: 60/371,330

10 April 2002 (10.04.2002) US

(71) Applicants (for all designated States except US): VIR-GINIA COMMONWEALTH UNIVERSITY [US/US]; 1101 East Marshall Street, Richmond, VA 23298-0568 (US). THE GOVERNMENT OF THE UNITED STATES THE DEPARTMENT OF VETERANS AF-FAIRS [US/US]; 810 Vermont Avenue, NW, Washington, DC 20420 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): DENT, Paul [US/US]; 10554 Boscastle Road, Glen Allen, VA23060 (US). GRANT, Steven [US/US]; 206 Desota Drive, Richmond, VA 23298 (US). KRYSTAL, Geoffrey [US/US];

9533 Pine Shadow Drive, Richmond, VA 23233 (US). YU, Chunrong [CN/US]; 901 Pump Road, Apt. 208, Richmond, VA 23233 (US).

(74) Agents: HOXIE, Thomas et al.; Novartis Corporate Intellectual Property, One Health Plaza, Bldg. 430, East Hanover, NJ 07936-1080 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SE, SG, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.

(84) Designated States (regional): Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMBINATION OF GLIVEC(STI571) WITH A CYCLIN-DEPENDENT KINASE INHIBITOR, ESPECIALLY FLAVOPIRIDOL IN THE TREATMENT OF CANCER

(57) Abstract: The present invention pertains to a combination for simultaneous, separate or sequential use which comprises (a) a cyclin-dependent kinase inhibitor and (b) 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide and to its use for the treatment of cancer, especially of Bcr/Abl* leukemia resistant to compound of formula (I).



hal Application No Ful/18 03/01418

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/506 A61K31/445					
According to International Patent Classification (IPC) or to both national classification and IPC B. FIELDS SEARCHED					
Minimum documentation searched (classification system followed by classification symbols)					
IPC 7 A61K					
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched					
Electronic data base consulted during the International search (name of data base and, where practical, search terms used)					
EPO-Internal, PAJ, BIOSIS					
	4 -	* *	·i		
C. DOCUME	ENTS CONSIDERED TO BE RELEVANT				
Category °	Citation of document, with indication, where appropriate, of the rel	evant passages	Relevant to claim No.		
χ	YU ET AL : "The cyclin dependant	kinase	1-16		
	inhibitor flavopiridol interatos		4		
	synergistically with the bcr/abl kinase inhibitor STI571 to induce mitochondrial				
	damage and apoptosis in bcr/abl+	human			
	leukemai cells (K562 and Lama-84)). "			
	vol. 98, no. 11, 2001, page 146a				
	XP002245420	l Florida			
	(Oral disclosure of 7-11/Dec 2001, Florida USA).				
	See whole document.				
		•\$•	27		
Furt	Further documents are listed in the continuation of box C. Patent family members are listed in annex.				
° Special ca	ategories of cited documents:	"T" later document published after the inte or priority date and not in conflict with	rnational filing date the application but		
"A" docum	ent defining the general state of the art which is not dered to be of particular relevance	cited to understand the principle or the invention	eory underlying the		
"E" earlier	document but published on or after the international date	"X" document of particular relevance; the cannot be considered novel or cannot	be considered to		
"L* document which may throw doubts on priority claim(s) or involve an inventive step when the document is taken alone which is clied to establish the publication date of another "V* document of particular relevance; the claimed invention					
citation or other special reason (as specified) cannot be considered to involve an inventive step when the document is combined with one or more other such document is combined with one or more other such document.					
P docum	means ent published prior to the international filing date but than the priority date claimed	ments, such combination being obvious to a person skilled in the art. 8 document member of the same patent family			
	actual completion of the international search	Date of mailing of the international sea			
	25 June 2003	10/07/2003			
Name and mailing address of the ISA		Authorized officer			
	European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk				
	Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cattell, James			

INTERNATIONAL SEARCH REPORT

ational application No. PCT/IB 03/01418

Box I Observations where certain clair	ns were found unsearcha	ble (Continuation of it	em 1 of first sheet)			
		• • • • • • • • • • • • • • • • • • • •				
This International Search Report has not been e	stablished in respect of certain	claims under Article 17(2)	(a) for the following reasons:			
1. X Claims Nos.: because they relate to subject matter no	ot required to be searched by t	his Authority, namely:				
see FURTHER INFORMATION	sheet PCT/ISA/210					
(4) (2語) 관 制作 (4)	. Fig.	说 景。 意。				
as the thing the	3) Digital 18	कः ः व्यव 'e .	(,2R % 3 4			
2. X Claims Nos.: because they relate to parts of the Inter an extent that no meaningful Internation	Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:					
see FURTHER INFORMATION	sheet PCT/ISA/210	**	•			
·:	*		¥			
3. Claims Nos.:						
because they are dependent claims and	d are not drafted in accordance	with the second and third	sentences of Rule 6.4(a).			
Box II Observations where unity of inve	ention is lacking (Continu	ation of item 2 of first	sheet)			
This International Searching Authority found mul	tiple inventions in this internation	onal application, as follows	:			
i.	Ş ₄ ,	· · · · · · · · · · · · · · · · · · ·	7			
	***	S. ESE				
As all required additional search fees w	vere timely paid by the applican	t, this International Search	Report covers all			
searchable claims.	ak ja		e ·			
As all searchable claims could be search of any additional fee.	ched without effort justifying an	additional fee, this Authori	ty did not invite payment			
' any additional fee.						
3. As only some of the required additional	search fees were timely paid t	by the applicant, this intern	ational Search Report			
covers only those claims for which fees	were paid, specifically claims	Nos.:				
٠.						
4. No required additional search fees were	e timely paid by the applicant.	Consequently, this internat	ional Search Report is			
restricted to the invention first mentione	ed in the claims; it is covered by	claims Nos.:				
:	a					
·	\.4					
Book and a Book at			ad by the englishmate areas			
Remark on Protest	I ne additional se	arch rees were accompanio	ed by the applicant's protest.			
	No protest accom	panied the payment of add	litional search fees.			
						

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 3-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

HLIC.

Continuation of Box I.1

Method for treatment of the human or animal body by therapy

Continuation of Box I.2

Present claims 1-9 adn 13-16 relate to a product/compound/method/apparatus defined by reference to a desirable characteristic or property, namely cyclin dependent kinase inhibitor

The claims cover all compounds having this characteristic or property, meaning that in the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the examples (flavopiridol)

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.